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(54) Title: CONTROLLED RELEASE TABLETS

(57) Abstract

The invention provides a controlled release tablet for the oral administration of a pharmaceutically active ingredient comprising a controlled release core composition comprising a pharmaceutically active ingredient incorporated into a polymeric carrier and diffusable therefrom at a predetermined controlled rate upon contact with a medium of an environment of use, the polymer carrier being insoluble in the medium; and a release rate controlling coating surrounding the core, the coating comprising a water insoluble and water impermeable polymeric material having at least one channeling agent dispersed in the coating and constituting about 5-60 wt./wt.% of the total coating, the channeling agent being soluble in the medium and being leachable from the coating upon contact with the medium to form molecular channels in the coating for passive diffusion of the pharmaceutically active ingredient via the channels at a controlled rate predetermined by the channels.

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CONTROLLED RELEASE TABLETS

The present invention relates to a controlled release tablet, which is useful for the oral administration of pharmaceutically active water soluble and water insoluble substances.

The controlled delivery of drugs from tablets have been described in numerous publications and products to do the same exist in the market.

As described, e.g., in U.S. Patent 5,178,868, "Drug release from a controlled release dosage form is generally controlled by a coating outside an active core. The release can be achieved

a) by diffusion: the coating swells in aqueous environment so that the active substance can diffuse through the stagnant liquid phase contained in the coating polymer; or

b) by osmosis: the coating is semi-permeable, i.e. only water can penetrate the coating polymer and dissolve the active substance, this will lead to a pressure buildup inside the coating, in order to allow the active to be released from the unit a hole or channel with a well defined area must be formed in the coating, this can be achieved either by laser drilling (SE patent 435 897 - U.S. Pat. No. 4,256,108 to Alza) or by incorporation of a substance which will form the channels by erosion after ingestion (U.S. pat. No. 4,687,660 and European patent application 0 171 457 to Wellcome), should the coating have any weak spots or cracks in it these will increase the release area and as a result give varying dissolution rates for different units, i.e. zero order release will not be achieved for the whole dose, or

c) by erosion: the coating will disintegrate by a process dependent on, e.g. enzymes or pH and leave the active core exposed to rapid dissolution.

The important of a pH independent diffusion with respect to obtaining a reproducible rate of availability and to minimizing intra- and inter-subject variations is known (GB patent 1,468,172 and Bechgaard & Baggesen, 1980). It is also known that controlled drug release in vivo can be achieved through an erodable process by enteric coating of a multiple units dosage form.

In said patent and in other U.S. patents such as U.S. Patent 4,629,619, 4,46,686, 5,458,887 and reissued patent 33,994, there are described different sustained release tablets incorporating a core coating which includes a pore forming material. However, none of said patents teach or suggest a controlled release tablet in which both the core and the coating provide for separate independent predetermined controlled rate release based on passive diffusion, as opposed to osmotic pressure, and assuring that even upon accidental damage or breakage of the coating, an accidental burst release of active ingredient will not occur.

Thus, according to the present invention, there is now provided a controlled release tablet for the oral administration of a pharmaceutically active ingredient comprising

a) a controlled release core composition comprising a pharmaceutically active ingredient incorporated into a polymeric carrier and diffusable therefrom at a predetermined controlled rate upon contact with a medium of an environment of use, said polymer carrier being insoluble in said medium; and

b) a release rate controlling coating surrounding said core, said coating comprising a water insoluble and water impermeable polymeric material having at least one channeling agent dispersed in said coating and

constituting about 5-60 wt./wt.% of the total coating, said channeling agent being soluble in said medium and being leachable from said coating upon contact with said medium to form molecular channels in said coating for passive diffusion of said pharmaceutically active ingredient via said channels at a controlled rate predetermined by said channels.

Thus, it will be realized that the tablet of the present invention is made up of two components, a controlled release core matrix that releases the entrapped drug in the proper releasing medium at a controlled manner without being disintegrated , preferably at a rate of up to **55%** during the first hour, up to **75%** at the second hour and at least **70%** of the drug during the next **5** hours.

The second component is a continuous polymeric coating that serves as a rate controlling membrane which releases the drug at a controlled rate of preferably not more than **70%** of the drug within **6** hours and not less than **70%** within **24** hours in the proper releasing medium.

The coating is preferably composed of a water insoluble polymer and a hydrophilic channeling agent that is leached out when exposed to the releasing medium. The water insoluble polymer may be a hydrophobic polymer that does not swell in water or a polymer that may swell in water. The channeling agent may be a water soluble small molecule such as sucrose and NaCl or a macromolecule such as polysaccharides, water soluble acrylic polymer, and other water soluble polymers.

In preferred embodiments of the present invention said channeling agent is a polysaccharide, and especially preferred for use as said channeling agent is arabinogalactan.

In especially preferred embodiments of the present invention there is provided:

1. A tablet that releases its entrapped active agent at a predetermined rate in a specified releasing medium, not more than 30% during the first hour, not more than 70% during 6 hours and not less than 70% of its drug content within 24 hours in the proper releasing medium;
2. A tablet that is composed of a slow release core matrix coated with a continuous water insoluble film containing a water soluble channeling agent that determines the drug release rate;
3. A tablet with a rate controlling film coating with a system that avoids an accidental burst release in case of a breakage of the coating;
4. A tablet in which the channeling agent is a branched polysaccharide such as Arabinogalactan; and
5. A tablet in which the coating is a water based dispersion of a water insoluble polymer with the channeling agent soluble in the water phase that form a continuous, uniform, stable, flexible and reproducible coating.

The pharmaceutically active ingredient in the formulations according to the present invention may be any active substance that is advantageously administered in a controlled release oral tablet formulation. Examples of suitable active substance are found among almost all therapeutic groups, including diuretics, antiepileptics, sedative, antiahrrythmics, antirheumatics, b-blockers, vasodilators, oral antidiabetics, antihypertensives, analgesics, bronchodilators, hormones, orally active peptides and proteins, vitamins, oral

antidiabetics, antibiotics, antihypertensives, anti-inflammatory agents, steroids, antifungals, antidepressants, homeopathic agents and enzymes.

As examples of active substances may be mentioned Diltiazem, nifedipin, ibuprofen, indomethacine, clonidine, KCl, lithium carbonate, depyridamol, paracetamol, verapamil, paracetamol, morphine, nitroglycerine, captopril, dexamethasone, propranolol, furoseamide, digoxin, and diclofenac.

Among these substances, some are characterized as having pH independent water solubility, other have a pH dependent solubility and some are water insoluble. According to this invention, water soluble drugs should be retarded by the core matrix and being released in a controlled pattern before applying the rate controlling coating. Accordingly, the insoluble drugs should be released from the core matrix at a proper rate which require a way to increase the availability of the drug when placed in the proper releasing medium. For this, the insoluble drug will be treated by physical means to increase its availability for example, blending the drug with a water soluble carrier (sugar, PEG) at a molecular level to meet the release specifications for the core matrix.

The core matrix is preferably in the shape of a common tablet (oval, circular, round edge rectangular) which is individually coated in the next step to provide the final tablet. The surface area may be between 20 and 200 mm and thickness of 1 to 10 mm or by weight of the core matrix in the range of 100 mg and 1500 mg. The composition of the core matrix depends on the nature of the drug. A hydrophilic drug is formulated with hydrophobic polymers that retard their availability while insoluble drugs are formulated with hydrophilic polymers that enable them to be released from the matrix

within the specification range. Water soluble drugs are typically granulated or compressed with one or more water insoluble polymers described for the coating. Examples of polymers are copolymers of methacrylic acid-methyl methacrylate and ethyl cellulose. Other ingredients that may be used in the core are bulking materials and binders. A water insoluble drug may be first solubilized in an organic solution containing a hydrophilic carrier [i.e. polyethylene glycol, low molecular weight poly(vinyl pyrrolidone) (PVP)] and sprayed on sugar microparticles to form granules with improved drug availability when contact with the releasing medium.

The coating polymer should have good film forming and adhesive properties, that can be applied either from an organic solvent or from a water dispersion. The amount of coating material applied on the core matrix is in the range of 5 to 50% of the weight of the matrix. The polymer used must be insoluble in water and water impermeable in order to prevent dissolution thereof and/or the creation of osmotic pressure within the tablet. Suitable polymers are non-swelling or slightly swelling cellulose alkyl ester or ether derivatives such as ethyl cellulose, methyl cellulose, cellulose acetate phthalate, methyl-hydroxypropyl cellulose; acrylic polymers such as copolymers of acrylic acid and Methylmethacrylate known as Eudragit family of polymers; vinyl polymers such as polyvinyl chloride, polystyrene, poly(vinyl acetate). The preferred polymers are water dispersions of methacrylic/methyl methacrylate polymers, Eudragit 30SE and ethyl cellulose, Aquacoat, or their acetone or alcohol solutions.

Preferably plastisizers also are present in the coating. The amount may vary between 1 and 30% by weight of the total coating solids, preferably between 5 and 20%. Examples of suitable plastisizers are acetyltributyl citrate, tributyl

citrate, triethyl citrate, blown castor oil, glyceryl triacetate, butyl sebacate and polyethylene glycol. The coating may contain coloring agents, flavor and any minor agents that makes the tablet more attractive for use.

The coating preferably contains a channeling agent in the amount of between 5 and 60% of the total coating solids. The channeling agent can be soluble in the coating liquid or microparticles dispersed in the coating liquid. When using a water base coating liquid, suitable channeling agents are pharmaceutically acceptable water soluble salts and sugars such as NaCl, boric acid, sodium borate, sucrose, lactose, and sodium lactate. Hydrophilic polymers such as linear and branched natural and modified polysaccharides such as dextran, arabinogalactan, synthetic polymers such as homo- and copolymer of vinyl alcohol, homo- and copolymers of acrylic acid, poly(ethylene glycol), poly(ethylene-co-propylene glycol), and poly(vinylpyrrolidone).

The coating is commonly applied on the core matrix by pan coating with spraying the water base or organic base coating liquid on the compressed matrices. Other methods such as fluidised bed and dipping methods may be used.

The channeling agent may be leached out to form channels through the film coating at different rates depending on the solubilization rate of the channeling agent in the releasing medium. In this regard, highly water soluble branched Arabinogalactan may be leached out from a coating more rapidly forming channels of a certain size and shape whereas less water soluble linear dextran may be leached out at a slower rate forming different channels which may affect the drug release rate.

The general procedure for producing the core matrix is by incorporating the pharmaceutically active ingredient in a mixture or granulate that will allow the controlled release of the active ingredient by passive diffusion at a specific rate predetermined by the core formulation by methods known per se from the core matrix. The preparation of the core matrix generally involves the granulation of the drug with a hydrophobic polymer (for water soluble drugs) using common granulation methods and then mixing the granules with ingredients that further retard or enhance the drug release from the matrix, a lubricant, or a colorant and compressing into tablets using common tableting machines. The general method of producing the coating according to the invention comprises the steps of dissolving or dispersing a hydrophobic polymer, channeling agent, plastisizer, colorant and other additives in water or in an organic solvent (alcohol, acetone). The coating dispersion is then applied on the core matrix tablets usually by a pan coating.

The core matrix is prepared by compression into a tablet granulates of the drug prepared from the drug and the retarding polymer.

While the invention will now be described in connection with certain preferred embodiments in the following examples and with reference to the accompanying figures, so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of

example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

In the figures:

Fig. 1A graphically illustrates the dissolution of Diltiazem from a coated tablet of Example 3a;

Fig. 1B graphically illustrates the dissolution of Diltiazem from a coated tablet of Example 3b;

Fig. 1C graphically illustrates the dissolution of Diltiazem from a coated tablet of Example 3c;

Fig. 1D graphically illustrates the dissolution of Diltiazem from a coated tablet of Example 3d;

Fig. 1E presents the dissolution of Diltiazem from a coated tablet of Example 3d in tabular form;

Fig. 1F graphically illustrates the dissolution of Diltiazem from a coated tablet of Example 3e (31% channeling agent) and 3f (33% channeling agent);

Fig. 1G presents the data of Figure 1f in tabular form; and

Figs. 1H and 1I tabularly and graphically represent the dissolution of verapamil from a coated tablet of Example 5. Dissolution release medium: buffer pH6.8 using a dissolution system-peddle mixing at 100 rpm. The results are an average of 6 chamber with a narrow standard deviation (less than 10%).

Example 1: preparation of core matrix for Diltiazem:

Granules of Diltiazem are prepared by spray granulation (using a Glatt spray granulation instrument) of a water dispersion of a hydrophobic polymer such as Eudragit RS30D containing a plastisizer such as an ester of citric acid. The drug may be mixed with hydrophobic or hydrophilic additives before granulation. The granules are mixed with common ingredients such as lactose and magnesium stearate (lubricant) and compressed into tablets using a Potary press, punches 11.0 (Q), 9.5 (R) without dividing line, tablet weight 350 to 500 mg each.

Typical compositions of core matrix mixtures:

a.

Granulation:	Diltiazem hydrochloride	240mg
	Aerosil 200	3mg
solution:	Eudragit RS30D water dispersion	30mg
(dry polymer)		
	Citroflex 2 (citrate ester plasticizer)	6mg
system:	Glatt spray granulator	

Matrix composition:	Diltiazem granules:	279mg
	Lactose DC	75mg
	Magnesium stearate	6mg

Dissolution release rate: 1h- 50 %, 2h- 68 %. 7h- 100 % carried out in a medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours using a dissolution system-peddle mixing.

b.

Granulation:	Diltiazem hydrochloride	240mg
	Eudragit L 100/55	80mg
solution:	Ethocel N100 in alcohol	15mg (dry polymer)
system:	Planetary mixer	

Matrix composition:	Diltiazem granules:	335mg
	Lactose DC	63mg
	Magnesium stearate	2mg

Dissolution release rate: 1h-36 %, 2h-47 %. 7h-70 % carried out in a medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours using a standard dissolution system-peddle mixing at 100 rpm. The results are an average of 6 chambers with a narrow standard deviation of less than 10%.

c.

Granulation:	Diltiazem hydrochloride	240mg
	Eudragit RS100	50mg
solution:	Ethocel N100 in alcohol	11mg (dry polymer)
system:	Planetary mixer	

Matrix composition:	Diltiazem granules:	335mg
	Lactose DC	64mg
	Magnesium stearate	2mg

Dissolution release rate: 1h-48 %, 2h- 64 %. 7h- 93 % carried out in a medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours using a dissolution system-peddle mixing.

d.

Granulation:	Diltiazem hydrochloride	240mg
	Aerosil 200	5mg
	Eudragit RS100	32mg
solution:	Eudragit RS30D	40mg (dry polymer)
	Citroflex 2	8mg
system:	Glatt spray	

Matrix composition:	Diltiazem granules:	325mg
	Lactose DC	25mg
	Magnesium stearate	6mg

Dissolution release rate: 1h- 48 %, 2h- 61 %. 7h- 87 % carried out in a medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours using a dissolution system-peddle mixing.

e.

Granulation:	Diltiazem hydrochloride	240mg
	Eudragit RS100	60mg
solution:	Ethocel N100 in alcohol	11mg (dry polymer)
system:	Planetary mixer	

Matrix composition:	Diltiazem granules:	335mg
	Lactose DC	140mg
	Magnesium stearate	4mg

Dissolution release rate: 1h- 52 %, 2h- 71 %. 7h- 100 % carried out in

a medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours using a dissolution system-peddle mixing.

Example 2: Core matrix for poorly soluble drugs

Nifedipin is a water insoluble drug which has some solubility in 0.1N HCl. For such drug, the purpose of the granulation step is to increase the drug dissolution rate from the matrix to meet the release characteristic determined for the core matrix. The granulation involve spraying an acetone solution of nifedipin with or without a hydrophilic component such poly(vinylpyrrolidone or poly(ethylene glycol) on a hydrophilic support such as lactose or avicel particles and compression molding the granules or mixtures containing the granules into tablets. The tablets are then coated with the rate limiting coating. Examples of granulation and tablet compositions are as follows:

a.

Granulation solution:	Nifedipine	300g (30mg/tablet)
	Acetone	6 litter solvent
	Povidone k-30	750g (75mg/tablet)
support:	Lactose 100 mesh size 3.0kg (300mg/tablet)	

preparation: the solution was sprayed on the lactose particles at 50°C for 1.5 hours using a Glatt. The granules containing 3.5% water were compressed into tablets.

Dissolution release rate in 0.1N HCl: 1h- 24 %, 2h- 40 %. 7h- 74 %

b.

Granulation solution:	Nifedipine	300g (30mg/tablet)
	Acetone	6 litter solvent
	Povidone k-30	250g (25mg/tablet)
	Primojel (Na starch glycolate)	200g (20mg/tablet)
	Hydroxypropyl methyl cellulose	200g (20mg/tablet)

support: Avicel PH-102 2.5 kg (250mg/tablet)

preparation: the solution was sprayed on the Avicel particles at 50oC for 1.45 hours using a Glatt instrument. The granules containing 3.8% water were compressed into tablets.

Dissolution release rate in 0.1N HCl: 1h- 25 %, 2h- 43 %. 7h- 78 %

c.

Granulation solution:	Nifedipine	300g (30mg/tablet)
	Acetone	6 litter solvent
support:	Lactose 100 mesh	3.0 kg (250mg/tablet)

preparation: the solution was sprayed on the Lactose particles at 50oC for 1.5 hours using a Glatt. The granules containing 3.1% water were compressed into tablets.

Dissolution release rate in 0.1N HCl: 1h- 22 %, 2h- 47 %. 7h- 80 %

d.

Granulation solution:	Nifedipine	300g (30mg/tablet)
	Acetone/ ethanol 3:2 v/v	5 liter solvent
	Primojel (Na starch glycolate)	150g (15mg/tablet)
	Hydroxypropyl methyl cellulose	150g (15mg/tablet)
	Povidon 750	750g (75mg/tablet)
support:	Dextrose	1600g (160mg/tablet)

preparation: the solution was sprayed on the Lactose particles at 75°C for 1.45 hours using a Glatt. The granules containing 3.7% water were compressed into tablets.

Dissolution release rate in 0.1N HCl: 1h-20 %, 2h-35 %. 7h-74 %

Example 3: Coating of Diltiazem core matrix tablets:

The core tablet of example 1e where coated by either a water base dispersion or by an organic base polymer solution (ethanol, isopropanol, acetone, methylene chloride). The channeling agents in this example are Siractan (a trade name for arabinogalactan) carried out in a dissolution release medium having a pH 2 for 2 hours, and then in a medium having a pH of 6.8 for an additional 5 hours, thereafter using a dissolution system-peddle mixing. The results are an average of 6 chambers with a narrow standard deviation (less than 10%).

Typical compositions per tablet are as follows:

a. Eudragit RL30D 1.5 parts
Eudragit RS30D 8.5 parts
Siractan 5.0 parts
Coating per tablet- 12 mg
Dissolution rate: see Figure 1A

b. Eudragit RL30D 2.0 parts
Eudragit RS30D 8.0 parts
Siractan 5.0 parts
Coating per tablet- 12 mg
Dissolution rate: see Figure 1B

c. Eudragit RL30D 1.0 parts
Eudragit RS30D 9.0 parts
Siractan 5.0 parts
Coating per tablet- 12 mg
Dissolution rate: see Figure 1C

d. Eudragit RS30D 10.0 parts
Eudragit RL30D 0.0 parts
Siractan 3.5 parts (BN 131095)
or 4.0 parts (BN 141095)
or 4.5 parts (BN 151095)
Coating per tablet- 20 mg
Dissolution rate: see Figure 1D

e. Eudragit RS30D 10.0 parts
Siractan 4.0 parts
Coating per tablet- 17 mg
Dissolution rate: see Figure 1E (BN 06119A)

f. Eudragit RS30D 10.0 parts
Siractan 5.0 parts
Coating per tablet- 20 mg
Dissolution rate: see Figure 1F (BN 06119B)

g. Aquacoat (dispersion of ethyl cellulose in water) 10.0 parts
Siractan 5.0 parts
Coating per tablet- 20mg
Dissolution rate: 3h-10%; 6h- 35%; 10h- 50%; 24h-90%

h. Ethyl cellulose in ethanol 10.0 parts
Siractan 5.0 parts
Coating per tablet- 20mg
Dissolution rate: 3h-5%; 6h- 25%; 10h-55%; 24h-90%

Example 4: Coating of Nifedipine core matrix tablets of Example 2a:
The tablets of example 1 where coated by either a water base dispersion or an organic base polymer solution (alcohol, isopropanol, acetone, methylene chloride).

Typical compositions per tablet are as follows:

a. Eudragit RS30D 8.0 parts
Eudragit RL30D 2.0 parts
Siractan 6.0 parts
Coating per tablet- 20 mg
Dissolution rate: 3h-5 %; 6h- 16 %; 10h- 30 %; 24h- 72 %

b. Eudragit RL30D 1.0 parts
Eudragit RS30D 9.0 parts
Siractan 10.0 parts
Coating per tablet- 20 mg
Dissolution rate: 3h- 15 %; 6h- 35 %; 10h- 60 %; 24h- 75 %

c. Aquacoat (dispersion of ethyl cellulose in water)10.0 parts (per dry polymer)
Siractan 6.0 parts
Coating per tablet- 20mg
Dissolution rate: 3h- 5 %; 6h- 22 %; 10h- 45 %; 30h- 80 %

Example 5: preparation of a coated tablet for Verapamil:

Granules of Verapamil are prepared by spray or wet granulation (using a Glatt spray granulation instrument or wet granulation device). The drug content in these tablets was 20 mg/tablet. The drug may be mixed with hydrophobic or hydrophilic additives before granulation. The granules are mixed with common ingredients such as lactose and magnesium stearate (lubricant) and compressed into tablets using a Potary press, punches 11.0 (Q), 9.5 (R) without dividing line, tablet weight 350 to 500 mg each.

The core tablet was coated by either a water base dispersion or by an organic base polymer solution (ethanol, isopropanol, acetone, methylene chloride). The channeling agents in this example is Siractan (a trade name for arabinogalactan). Other channeling gents such as dextran can be used.

Typical compositions of core matrix mixtures:

Granulation:

Verapamil HCl	240mg
Methocel K4M (hydroxypropyl methyl cellulose)	25mg
Lactose DC	78mg

Granulation using water as solvent

Matrix composition:

Verapamil granules	343 mg
Aerosil 200	2 mg
Lactose DC	40 mg
Magnesium stearate	4 mg

Equipment: High shear mixer

Dissolution rate: 1h- 44%; 2h- 72%; 7h- 97%

Dissolution in buffer pH6.8 in a paddle dissolution system at 100 rpm.

Coating:

Citroflex 2	5.0mg
Eudragit RL30D	1.2mg (per dry polymer)
Eudragit RS30D	10.8mg (per dry polymer)
Talc	8.0mg
Siractan	6.0mg

Dissolution rate: see Figure 2.

Dissolution in buffer pH6.8 in a paddle dissolution system at 100 rpm.

It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative examples and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

WHAT IS CLAIMED IS:

1. A controlled release tablet for the oral administration of a pharmaceutically active ingredient comprising

a) a controlled release core composition comprising a pharmaceutically active ingredient incorporated into a polymeric carrier and diffusable therefrom at a predetermined controlled rate upon contact with a medium of an environment of use, said polymer carrier being insoluble in said medium; and

b) a release rate controlling coating surrounding said core, said coating comprising a water insoluble and water impermeable polymeric material having at least one channeling agent dispersed in said coating and constituting about 5-60 wt./wt.% of the total coating, said channeling agent being soluble in said medium and being leachable from said coating upon contact with said medium to form molecular channels in said coating for passive diffusion of said pharmaceutically active ingredient via said channels at a controlled rate predetermined by said channels.

2. A controlled release tablet according to claim 1, wherein said core comprises a plurality of compacted granules having said active ingredient dispersed therein

3. A controlled release tablet according to claim 1, wherein said core comprises a plurality of compacted granules having said active ingredient encapsulated therein.

4. A controlled release tablet according to claim 1, wherein said core is formulated to release said active ingredient at a rate of up to 55% during the

first hour, up to 75% during the second hour and at least 70% of the drug during the next five hours.

5. A controlled release tablet according to claim 1, wherein said coating is formulated to release up to 70% of said active ingredient within six hours, and at least 70% within 24 hours.

6. A controlled release tablet according to claim 1, wherein said channeling agent is a polysaccharide.

7. A controlled release tablet according to claim 1, wherein said channeling agent is arabinogalactan.

8. A controlled release tablet according to claim 1, wherein said channeling agent is dissolved in said coating.

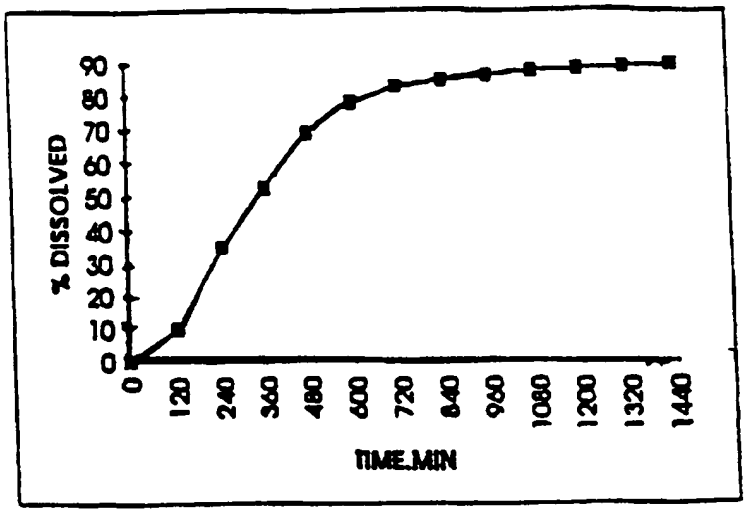

FIG. 1C

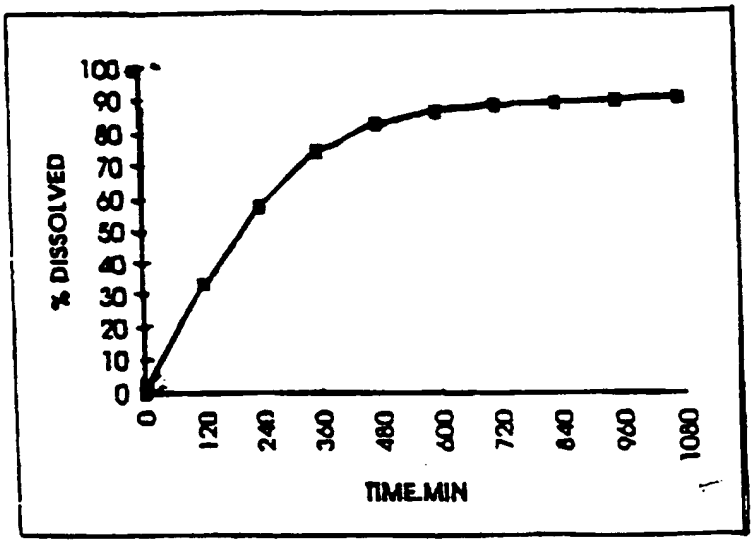

FIG. 1B

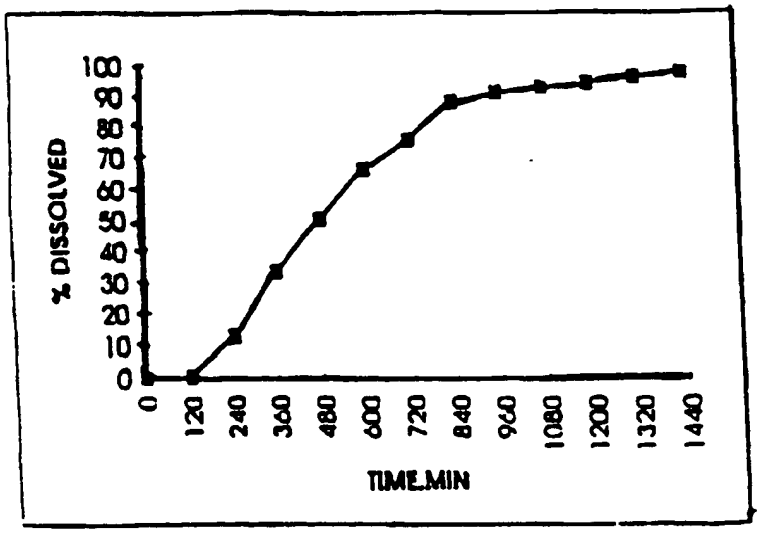

FIG. 1A

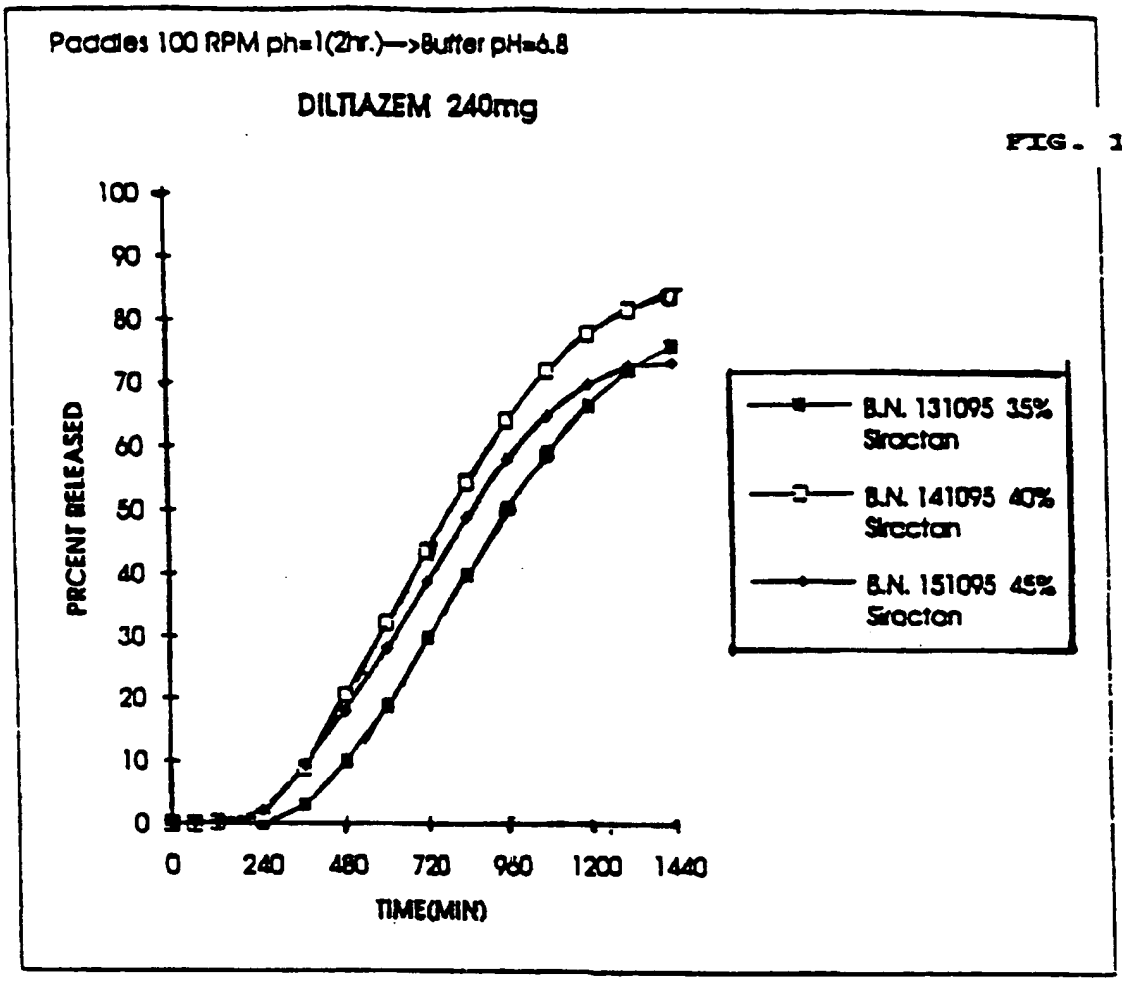

FIG. 1D

DILTIAZEM 240mg Paddles 100 RPM pH=1(2hr.)--->Buffer pH=6.8			
TIME(min)	B.N. 131095 35% Sractan	B.N. 141095 40% Sractan	B.N. 151095 45% Sractan
0	0	0	0
60	0.2	0	0.2
120	0.1	0.2	0.3
240	0	1.1	2
360	2.9	8.8	9.3
480	9.9	20.4	17.9
600	18.8	32.1	27.9
720	29.5	43.6	38.7
840	39.8	54.5	48.9
960	50.4	64.2	58
1080	58.9	72.1	64.9
1200	66.5	78	69.9
1320	72.3	81.6	72.8
1440	75.9	83.8	73.3

FIG. 1E

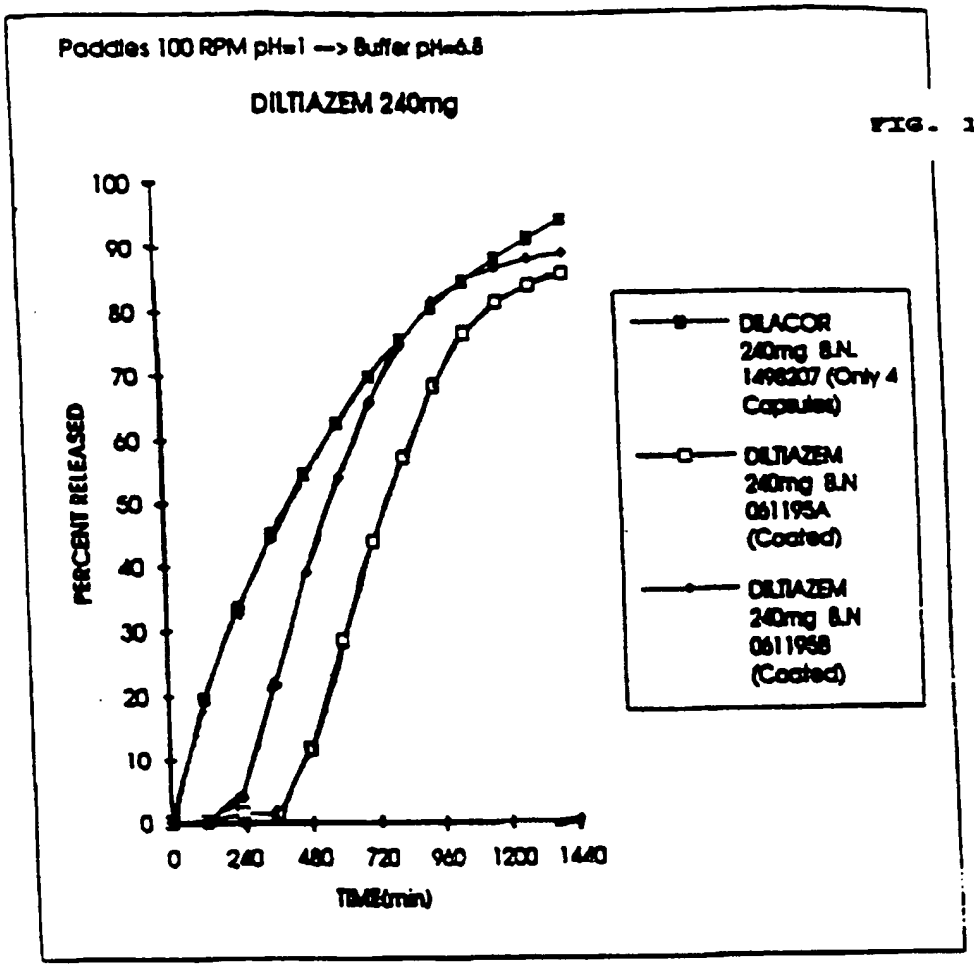

FIG. 1F

DILTIAZEM 240mg PADDELS 100 RPM pH=1(2hr.) --> Buffer pH=6.8			
TIME (min)	B.N. 1498207 (Only 4 Capsules)	DILTIAZEM 240mg B.N 061195A (Coated)	DILTIAZEM 240mg B.N 0611958 (Coated)
0	0	0	0
120	19.6	0.2	0.4
240	33.23	1.5	3.9
360	44.83	1.2	21.7
480	54.33	11.6	39
600	62.53	28.4	53.9
720	69.63	43.8	65.7
840	75.53	57.2	74.6
960	80.45	68.3	81.3
1080	84.5	76.5	84.7
1200	87.93	81.3	86.5
1320	91.03	83.8	87.9
1440	93.88	85.6	88.8

FIG. 1G

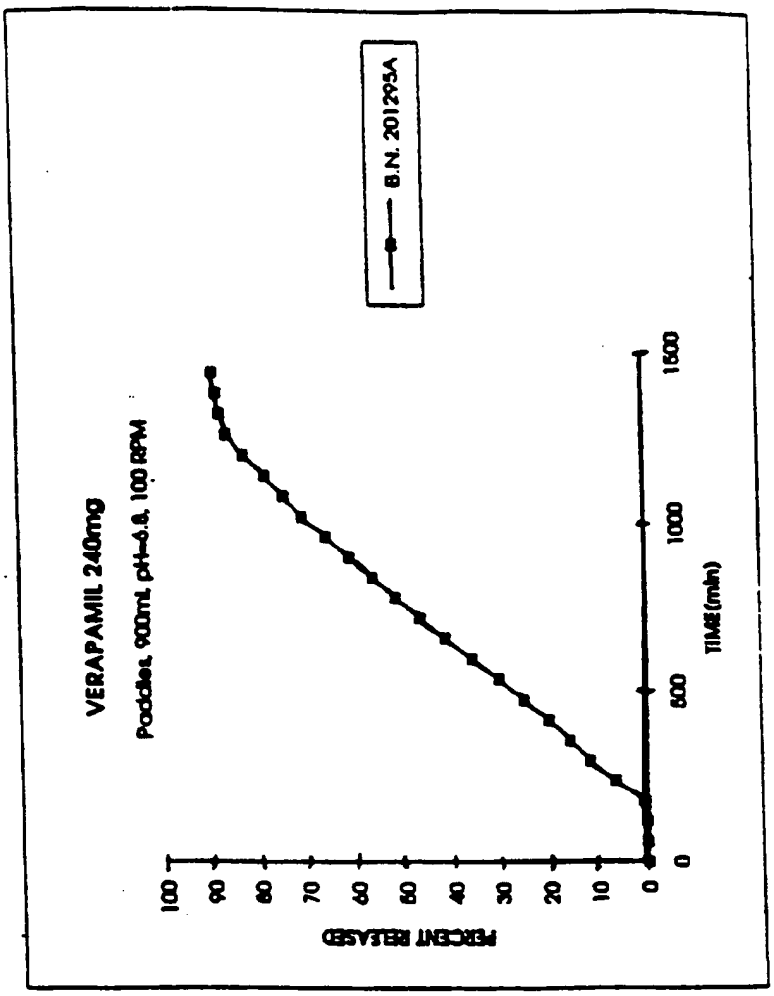

FIG. 1I

VERAPAMIL 240mg Paddles, 900ml, pH=6.8, 100 RPM	
TIME(min)	B.N. 201295A
0	0
60	0.1
120	0.1
180	0.6
240	6.5
300	11.5
360	15.6
420	19.8
480	24.8
540	30
600	35.6
660	41.2
720	46.3
780	51.3
840	56.1
900	60.9
960	65.6
1020	70.4
1080	74.2
1140	78.1
1200	82.6
1260	86.2
1320	87.5
1380	88.2
1440	88.9

FIG. 1II

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 97/01770

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/28 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 42 30 563 A (BOEHRINGER INGELHEIM KG) 17 March 1994 see page 2, line 14 - line 62 see page 3, line 3 - line 8 see page 3, line 62 - line 63 ---	1,2,8
X	US 5 458 887 A (CHIH-MING CHEN ET AL.) 17 October 1995 cited in the application see the whole document ---	1,2,8
X	GB 2 218 905 A (ELAN CORPORATION PLC) 29 November 1989 see page 6, line 11 - page 8, line 2 see page 9, line 1 - page 10, line 20 --- -/--	1,3,5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 October 1997	17. 10. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alvarez Alvarez, C

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 97/01770

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	EP 0 314 206 A (MERCK & CO. INC.) 3 May 1989 see page 9, line 2 - line 5	6,7

1

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INTERNATIONAL SEARCH REPORT

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